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ABSTRACT

This report summarizes research and training activities between 1984 and 1987 of the Pregnancy and Perinatology Branch of the National Institute of Child Health and Human Development. Activities are reported for the following six maternal-infant emphasis areas: (1) high risk pregnancies; (2) fetal pathophysiology; (3) premature birth and labor; (4) disorders of the newborn; (5) Sudden Infant Death Syndrome; and (6) Acquired Immune Deficiency Syndrome. The Branch supported research in these areas including awarding approximately 32.4 million dollars in 236 grants and contracts during Fiscal Year 1986. Highlights of research supported is summarized for each of these areas. Also reported is research training, provided through Individual Postdoctoral Fellowships and Institutional Research Training Grants. Recent research supported by the Branch through the Perinatal Emphasis Research Centers is noted. Briefly reviewed are the Branch's Cooperative Agreements, the Contract Program, and the Small Business Innovative Research Program. Finally, planned future research emphases in the six areas are reported. Various figures detail funding distribution and several tables present specific funding data by category. (DB)

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REPORT TO

THE NATIONAL ADVISORY CHILD HEALTH AND HUMAN DEVELOPMENT COUNCIL

PREGNANCY AND PERINATOLOGY BRANCH
CENTER FOR RESEARCH FOR MOTHERS AND CHILDREN
NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

JUNE 1987

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INTRODUCTION

> "Life is lengthened, its existence rendered less painful and more hopeful and its ailments so much reduced by what has already been accomplished, that — given what is wanted in time and in freedom of research — there seem to be scarcely any limits to the good we may predict for future generations."
>
> J. Russel Raynolds
> The Lancet, 2:650, October 1, 1887

This report from the Pregnancy and Perinatology Branch (PPB) coincides with two important historical events: The Centennial of the National Institutes of Health (NIH) and the soon to be celebrated 25th Anniversary of the National Institute of Child Health and Human Development (NICHD). Public Law 87-838 (October 17, 1962) authorized the establishment of "an Institute for the conduct and support of research and training relating to maternal health, child health and human development, including research and training in the special health problems and requirements of mothers and children, and in the basic sciences relating to the processes of human growth and development, including prenatal development." Since then research and training in the areas of pregnancy, fetal development and neonatal medicine have been supported by various Branches within the Institute. Although the Institute's first organizational chart did not identify a specific Branch on pregnancy and perinatology, 89 grants awarded at the first two NICHD Council meetings (November 1963 and March 1964) addressed questions that today would have been assigned to the PP Branch.

The Pregnancy and Perinatology Branch was established in December 1984 as part of the Center for Research for Mothers and Children. The Branch assumes primary responsibility for research aimed at improving outcome of pregnancy and the neonatal period. Other components of the Institute also support research relevant to this goal. Communication between programs within and outside of the NICHD leads to coordinated approaches in some areas and to the consolidation of efforts towards the solution of multifaceted problems. Within NICHD this activity is facilitated by the close interaction of the five Branches grouped under the umbrella of the Center for Research for Mothers and Children (CRMC) (Figure 1).

The previous report to Council took place in September 1984. This report will attempt to present an overview of research and training activities and accomplishments in maternal and infant health and summarize plans for the future.

PROGRAM OVERVIEW

> "As with all sciences, the advances in medicine have been by means of discoveries, improvements, and added facts which have marked epochs in its history. In medicine, as in other sciences, there are still many worlds to be conquered, many mines to be explored, and many virgin fields to be turned up and cultivated."
>
> Medicine in 1936 (a 50-year projection)
> JAMA, July 31, 1886

Activities of the Branch are organized around six maternal-infant emphasis areas, which complement each other and must be viewed as a comprehensive approach to research during the pre-, peri- and postnatal periods. These are:

(1) High-Risk Pregnancies: Over the last 20 years significant progress has occurred in maternal survival and well-being which has surpassed improvements in fetal outcome. Research efforts on high-risk pregnancy are directed towards the closure of this gap while continuing studies in both normal and abnormal pregnancies.

(2) Fetal Pathophysiology: Studies in fetal pathophysiology are examining the factors influencing normal and abnormal embryonic development. Efforts focus on normal and abnormal development at the molecular, tissue, and organ levels. Emphasis is placed on studies facilitating the assessment of fetal status to provide meaningful antenatal diagnosis. Another area of special interest examines the mechanisms responsible for intrauterine growth retardation and its consequent increased morbidity and mortality.

(3) Premature Birth and Labor: Premature labor and birth is a major cause of neonatal mortality and morbidity. Two-thirds of all infant mortality occurs among infants weighing 2,500 grams or less at birth. Furthermore, the nation's high prematurity rate is responsible for our relatively high infant mortality compared to other countries. Consequently, this program supports studies of the normal onset of labor, the reasons for premature labor, and how premature labor might be stopped without detrimental effects.

(4) Disorders of the Newborn: Disorders of the newborn are responsible for approximately three-fourths of the infant deaths in the United States, and produce long-term disability for many individuals who are affected by them and survive. Research directed towards reducing the impact of these disorders includes studies of maternal health problems that affect the status of the infant, adaptation of the newborn infant to its environment, and problems in the early weeks of life that influence subsequent development and behavior.

(5) The Sudden Infant Death Syndrome (SIDS): The NICHD has made particular efforts to encourage research on SIDS since 1974. Research has demonstrated that the SIDS infant no longer can be viewed as having been perfectly healthy prior to death, but rather is believed to have had developmental abnormalities. Current research efforts are directed towards identifying the cause or causes of these abnormalities in postnatal development.

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(6) Acquired Immune Deficiency Syndrome (AIDS): The increasing number of women and infants infected by human immunodeficiency virus (HIV) call for research to understand the magnitude of the problem and to determine the efficacy of potential therapeutic approaches.

The Branch uses a number of mechanisms for the support of research. During FY'86, it awarded a total of 236 grants and contracts amounting to approximately 32.4 million dollars (Table 1). As shown in Figure 2, these funds were distributed among the six problem areas as follows: high-risk pregnancy (32 percent), fetal pathophysiology (29 percent), premature labor and birth (15 percent), disorders of the newborn (21 percent), and the sudden infant death syndrome (3 percent). Maternal and child AIDS research is now being organized. Program holdings (comparing FY'80, FY'83, and FY'86) for each area are shown in Figure 2, and comparisons of support mechanisms are depicted in Figure 3. The apparent decrease of direct SIDS support is compensated for by an increase in the areas of fetal pathophysiology and disorders of the newborn. Research in these two components of the portfolio is of importance to the overall understanding of sudden infant death.

As seen in Figure 4, grants and contracts are awarded to investigators in both clinical (67 percent) and nonclinical or basic science (33 percent) departments. Analysis of awards to clinical departments shows the following distribution (Figure 5): obstetrics and gynecology, 29 percent, pediatrics, 28 percent, and other clinical departments, 10 percent. The overall distribution of Principal Investigators shows a higher number of M.D.'s than Ph.D.'s (M.D. degree, 54 percent, Ph.D. degree, 37 percent, and non-doctorate degree, 4 percent). The non-doctorate degrees correspond to investigators awarded a small business innovative research grant. An analysis of the distribution by gender, degree, and department shows that 83 percent of the principal investigators are male and 17 percent are female. These numbers remain similar to those tabulated for FY 1983. Further analysis of the Principal Investigators distribution by department is presented in Figure 6. Actual numbers and funds are shown in Table 2.

RESEARCH TRAINING

> "Should the millenial day come when everyone who elects to study medicine must go through a thorough preliminary course of training for it, it is to the experimental sciences that we must look for the foundation upon which to build a thoroughly competent physician."
>
> Scientific Education for Medicine
> JAMA, January 9, 1886

Research training continues to be provided through two types of grants: Individual Postdoctoral Fellowships (F32s, F33s, F34s) and Institutional Research Training Grants (T32s). In 1986, thirteen T32s were active, supporting 50 scientists (2 predoctoral, 48 postdoctoral), a majority in Departments of Pediatrics (9), 3 located in Departments of Obstetrics, and 1

in a non-clinical Department (Table 4). Three years ago, it was noted that a forty-three percent decline in individual fellowships (F32s) had occurred since 1980. Table 3 shows that a thirty-seven percent increase over 1983 is recorded for 1986, but these fluctuations involve only three to five individuals due to the modest number of F32s awarded.

The Branch also supported 17 Research Career Programs in FY'86. Although some Special Emphasis Research Career Awards (KO_1 or SERCAs) are still being supported, this type of award has been discontinued. The KO_4 (Research Career Development Award) and KO_8 (Clinical Investigator Award) continue to be supported and 12 awards are active. A new award, the K_{11} (Physician Scientist Award) received a good response from potential applicants and two are currently funded. The KO_4 fosters the development of young scientists with outstanding research potential for careers of independent research in the sciences related to health. The KO_8 provides the opportunity for promising clinically trained individuals with demonstrated aptitude for research to develop into independent biomedical investigators in several clinical areas relevant to maternal and child health. Finally, the K_{11} encourages individuals with clinical training to develop research skills in a fundamental science and become independent investigators.

An innovative cooperative agreement has been awarded recently to the Association of Medical School Pediatric Department Chairman (AMSPDC) to support a Pediatric Physician Scientist Program. The program involves five years of training; two years of basic research training funded by NICHD and/or other private agencies and three years funded by the sponsoring institution in a junior faculty position with guaranteed seventy-five percent free time for research under an identified preceptor. The program is administered by a Task Force representing the AMSPDC, NICHD, and participating private agencies. Selection of applicants and designation of appropriate training laboratories is being carried out by specific subcommittees. The first meeting for the selection of applicants took place in March 1987 and the second group of applicants were interviewed at the time of the American Pediatric Society/ Society for Pediatric Research (APS/SPR) meeting in April 1987.

RESEARCH GRANTS HIGHLIGHTS

HIGH-RISK PREGNANCY

> "The past year has been productive of a large number of papers, many of which represent honest, earnest, and able investigation . . . . . in Obstetric Medicine."
>
> The Annus Medicus 1887
> Lancet, 2:1319, December 31, 1887

Maternal physiologic adaptations during pregnancy continue to attract investigator interest. For example, although cardiac output increases significantly during mid-pregnancy, it falls to prepregnant levels in late gestation in the human. Investigators in one program project sought to

discover whether stroke volume (amount of blood ejected from the heart per contraction) was decreased in the late pregnancy because of inadequate venous return to the heart, or alternatively, by reduced ventricular function. Observations of cardiac output, heart rate, and stroke volume obtained by impedance cardiography were studied for all three trimesters and postpartum, at rest, during and following bicycle exercise. Results indicated that heart contractility was not different in late pregnancy compared to postpartum values. Thus, limitations of cardiac filling appear to be important physiologically in late pregnancy. Accordingly, the investigators are pursuing whether venous return is impaired by mechanical obstruction of venous flow by the enlarged uterus, by changes in venous tone, or both.

Hypertension induced by pregnancy is associated with elevated maternal and fetal morbidity and mortality. Unfortunately, effective and rational therapy has been elusive because the physiological changes occurring in this condition are inadequately understood. Currently, considerable research on this problem is focused on altered prostaglandin metabolism. In pregnant sheep, for example, one investigator has found that infusions of prostaglandin E_2 produce increased sympathetic vasomotor stimulation, hypertension, and increased uteroplacental blood flow. Thus, this finding may represent a new animal model which can be used to study the effects of sympathetic-mediated hypertension in pregnancy. The same investigator has also studied the ability of another prostaglandin (I_2) to lower blood pressure in animals rendered hypertensive during pregnancy by unilateral renal artery occlusion. He found that PGI_2 reduces blood pressure in this model, but not uterine vascular resistance, resulting in a significant decrease in uteroplacental blood flow and a fall in fetal oxygenation. These results are timely because some clinical investigators have suggested that pregnancy-induced hypertension in humans is due to reduced prostacyclin (PGI_2) production and therefore could be treated with PGI_2 or a PGI_2 analog. However, this animal study suggests that administration of prostacyclin to treat gestational hypertension may entail significant risk to the fetus.

An estimated 16 million Americans are affected with gallstones. The prevalence is higher in women than men, and higher in women with greater numbers of pregnancies. The prevalence is also higher in women receiving oral contraceptives or postmenopausal estrogen replacement. An unusual type of jaundice in pregnancy occurs because of poor bile excretion in certain women who are extremely sensitive to estrogens, during pregnancy and during oral contraceptive use. Estrogens also have an inhibitory effect on drug elimination by the liver. One investigator seeks to understand the mechanisms whereby estrogen exerts such effects by a series of animal and cellular studies. She has already demonstrated in the rat model that specific metabolites of the significant estrogens—the D-ring glucuronide conjugates—are potent inhibitors of bile flow. Further studies are designed to elucidate how the toxic estrogen metabolites may alter (1) uptake of bile acids by liver cells, (2) metabolism of bile acids, and (3) excretion of bile acids. Such studies have direct applicability to the issue of the rational use of therapeutic drugs, and of drug toxicity, in pregnancy. In addition, better understanding of gallstone formation in pregnancy may lead to opportunities for their prevention.

It is established that maternal smoking causes fetal growth retardation and increases the risk of pregnancy complications. However, the mechanisms by which these effects are produced have eluded researchers. It is known that cadmium is one of the toxic agents in cigarette smoke, and animal studies have suggested that fetal growth can be retarded by cadmium. It is also known that cadmium accumulates in certain organs (such as the kidney, liver, and placenta) and that this phenomenon is associated with an accumulation of zinc as well. It is also known that the zinc nutritional status of pregnant women is often marginal. From these reports, one investigator developed a hypothesis that there is a sequestration of zinc in the placenta of pregnant women who smoke, with resulting fetal zinc deficiency, and in turn, impaired fetal growth and development. Data from 200 patients have confirmed significant, positive correlations between maternal smoking (as documented by thiocyanate levels) and levels of cadmium in whole blood and placenta, and in zinc levels in placenta. Infants of smoking mothers had decreased zinc levels in red blood cells and were of lower birth weight. There was no difference in dietary zinc intake between smokers and non-smokers. These results support the hypothesis of a cadmium-zinc interaction in pregnant women who smoke. The investigator is designing a study to see if zinc supplementation in smokers during pregnancy can improve the placental transfer of zinc to the fetus and thereby increase birth weight.

FETAL PATHOPHYSIOLOGY

> "May it not be that the twentieth century will witness, among other good things, a wonderful extension and development of beneficent Antenatal Therapeutics."
>
> Ballantyne, John W.
> Manual of Antenatal Pathology and Hygiene - The Fetus
> W. Wood, New York, 1902

Progesterone and estrogen (estradiol) are essential to the maintenance of pregnancy in many species and cortisol of fetal adrenal origin is essential to fetal maturation, especially of the lungs. Although the actions of these hormones are reasonably defined, factors regulating their production by the fetoplacental unit are poorly understood. Thus, a research project is studying the regulation of hormone metabolism in the baboon, whose endocrinology is similar to the human. These investigators have found that placental production of progesterone is dependent on estrogen, and their report was the first to document that another endogenous hormone modulates progesterone production in mid- and late primate pregnancy. Further, this group has found that the fetus is important in placental progesterone production. Such a role for the fetus was suggested by experiments in which baboon fetectomy (removal of the fetus, but not the placenta) resulted in loss of estrogen formation and a marked decline in maternal progesterone. After fetectomy, the placenta was shown to remain intact functionally. This research group plans to examine whether estrogen regulates placental progesterone production in vivo by enhancing formation or by reducing catabolism of progesterone. Also, a culture system of baboon placental cells

will be used to study numerous potential regulation factors for their effects on progesterone production by the cultured cells. It is expected that insights gained with the in vitro system can be used to design additional in vivo experiments in baboons.

Another research team is embarked on the elucidation of the mechanism responsible for the early increase in serum T_3 during the transition from fetal to neonatal life. Their study with acutely thyroidectomized newborn lambs has shown that the thyroid gland is the major source of T_3 in the immediate newborn period.

Fetal growth factors are being studied for their role in normal growth, as well as in abnormal conditions. One investigator has found that somatomedins appear to act at or near their sites of cellular synthesis, that is, in a so-called autocrine or paracrine manner. This view is based on experiments which show that tissue levels of somatomedin C-insulin-like growth factor I (Sm-C/IGF-I) in rat fetus rise before blood concentrations rise in response to growth hormone administration. Such insight was preceded by improvements in assay techniques, by the same investigator, which permitted reliable assays of low tissue concentrations of Sm-C/IGF-I in the small amounts of tissue available from the fetus. By using in situ hybridization histochemistry, an investigator determined that somatomedin messenger RNAs were localized in connective tissues or cells of mesenchymal origin in many organs and tissues from human fetuses (16 to 20 weeks gestation). This finding facilitates the understanding of fetal growth as these cells, being widely distributed and anatomically integrated into tissues and organs, are ideally located for production of somatomedins which may exert paracrine effects on nearby target cells. In an animal model of intra-uterine growth retardation produced by uterine artery ligation in pregnant rats, serum, lung, and liver concentrations of Sm-C/IGF-I correlated very well with the degree of growth retardation. This and other experiments suggest the probable strong influence of nutrition on somatomedins. Other studies will attempt to clarify which tissues produce somatomedins and when they are generated in the fetus and newborn.

Postnatal growth of lung parenchyma in cats was shown to depend on respiratory muscle activity. A further step toward understanding the responsible mechanism is the demonstration that stress forces (pulmonary distending pressure) regulate postnatal cell proliferation in lung parenchyma through the mitogenic activity of somatomedin. Somatomedins are insulin-like peptide growth factors whose concentration in postnatal serum are growth hormone dependent. Somatomedins were found in most human fetal tissues at midtrimester, localized in specific cells.

Other studies are examining the relationship between growth patterns and oxygen availability using chick embryos. Previous work has shown that those exposed briefly to 60% O_2 weighed significantly more than control embryos maintained in air (normoxic - 21% O_2) and that they exhibited a stimulation of metabolism. Current studies demonstrate that limitation of oxygen availability by exposure to 15% O_2 retards embryonic growth and metabolism. Therefore, growth and metabolism of the normoxic chick embryo late in development are limited by oxygen availability.

Understanding the pattern of physiological maturation in utero and the adjustments needed to adapt to extrauterine life is basic to facilitate the development of diagnostic and therapeutic approaches to fetal and neonatal problems. A research team is examining the perinatal development of renal function and metabolism in sheep. In the fetus, the response observed to acute decrease in oxygenation was a marked diminution in arterial oxygen tension and content without a change in renal blood flow. Oxygen delivery decreased markedly while renal oxygen extraction increased and oxygen consumption decreased proportionally to oxygen availability. Those findings indicate that renal oxygen consumption in the fetus is sensitive to the rate of oxygen delivery rather than to blood flow or arterial oxygen content. The transition to extrauterine life was accompanied by an increase in both renal function and metabolic rate.

Pulmonary surfactant deficiency has been clearly recognized as responsible for the respiratory distress syndrome in the newborn. The synthesis of the surfactant phospholipids and lung maturation in utero have been extensively studied. Corticosteroids are thought to be one of the major triggering hormones for the onset of surfactant maturation. An investigator is studying the effect of various hormones on lung phospholipid biosynthesis and has shown that dexamethasone (a steroid) stimulates fatty acid synthesis in fetal lung and that both the normal developmental increase and the dexamethasone-induced increase are prevented by tri-iodothyronine (T_3). Thus, although dexamethasone and T_3 have some common effects in the fetal lung they also have opposing effects.

Ongoing studies in the pregnant ewe are assessing the role of hepatic glycogen metabolism in fetal and maternal glucose homeostasis during a prolonged fast. It was shown that during fasting, the pregnant ewe depletes her hepatic glycogen stores in association with a reduction in glycogen catabolizing enzyme activity. In contrast, the fetus does not consume its glycogen reserves during hypoglycemia (associated with maternal fasting), possibly preserving these stores for postnatal use.

PRETERM LABOR AND BIRTH

> "It is doubtful, however, if any 12 hours after birth are just so full of possibilities, physiological and pathological, as is the time during which the fetus is passing through the maternal canals . . . Birth, it must be remembered, does not mark a beginning, but a stage in life's progress . . ."
>
> Ballantyne, John W.
> Manual of Antenatal Pathology and Hygiene - The Fetus
> W. Wood, New York, 1902

It is likely that prostaglandins (PG) play an important role in human parturition, because prostaglandins: (1) increase strikingly in concentration during labor in amniotic fluid and maternal blood; (2) are synthesized by placental and uterine tissues; (3) can act to induce labor in women at any stage of gestation.

Also, inhibition of PG synthesis during pregnancy causes a delay in the onset of labor. Prostaglandins are metabolic products of arachidonic acid (AA) by the cyclooxygenase pathway. Another AA pathway, via lipoxygenase, leads to metabolic products which appear to have a potential role in utero-placental perfusion and in contractile activity of the uterus. These products are the HETEs (hydroperoxy-dico-hydroxy-eicostetranoic acids). The lipoxygenase and cyclooxygenase pathways seem to interact with one another. For example, the HETEs inhibit prostacyclin (PGI) biosynthesis and hence, their abnormal intrauterine production may be important in the pathogenesis of pregnancy-induced hypertension, which is a condition associated with reduced PGI formation. Preliminary evidence also suggests a metabolic shift near term by human amnion cells away from the lipoxygenase and towards the cyclooxygenase pathways, thereby enhancing the formation of prostaglandins which are known to produce labor. Research is now focusing on factors that can regulate these various metabolic pathways. Interleukin 1 is an inflammatory mediator that may be the mechanism whereby intrauterine infection results in preterm labor and birth. In vitro studies have shown that interleukin 1 can be a stimulator of prostaglandin production.

Oxytocin is the most potent natural stimulator of uterine contractions at term. However, because of low systemic concentrations of oxytocin in the mother prior to labor, the hormone has been thought important only for the later, "expulsive" phase of labor. One investigator, using an animal model, sought to understand why the pregnant uterus at term becomes markedly sensitive to oxytocin. He found an abrupt increase in the oxytocin receptor concentration in the uterine muscle. In his rat model, there is a clear correspondence between receptor number and sensitivity. Although comparable experiments have not been possible in human uteri, it has been found that women who were not responsive to oxytocin had relatively low oxytocin receptor levels. Alternatively, women in preterm early labor had receptor levels in the uterus that were equivalent to women in early labor at term. Thus, labor may be initiated, in part, by the up-regulation of oxytocin receptors. Also, the work illustrates that the endocrine status of an individual cannot necessarily be determined from circulating hormone levels alone.

Another researcher has reported a close temporal relationship between the oxytocin sensitivity change and a marked increase in prostaglandin (PGF_2) production by the uterus in the rat model. Suppression of in vivo PG synthesis caused a reduction in both spontaneous uterine contractility and oxytocin-induced contractions. Thus, prostaglandins probably play a role in modulating the effect of oxytocin.

It has also been found that oxytocin can stimulate prostaglandin production in decidua, the tissue lining the placenta and membranes. The prostaglandin may cause uterine contractions directly, or potentiate the oxytocic effect, or even promote cervical dilatation. Thus, the complex interactions of the system for controlling uterine contractile activity are only beginning to be understood. It has been difficult to unravel the respective roles in labor for some of the controlling factors because it has not been possible completely to deprive an animal model of one of the putative factors, such as oxytocin. However, the second investigator cited above has also prepared a

number of oxytocin antagonists, which are slight chemical modifications of the natural molecule. These antagonists have the potential to occupy oxytocin receptors and prevent natural oxytocin from reaching them and producing the usual effects that are associated with the initiation and maintenance of labor. Studies with such antagonists are in progress.

DISORDERS OF THE NEWBORN

> "Humanity is ready to bow at the footstool of science, and beg, that the ratio between those who live and those who die at the tender age be diminished and that they have thrown around them the protecting care of medicine."
>
> W.D. Haggard, M.D.
> JAMA, VII, 3, July 3, 1886

In 1984, NICHD launched a major special initiative: an expanded research program in the prevention of low birth weight. This important problem in maternal and child health may be the consequence of intrauterine growth retardation (IUGR), premature labor, or both. Most infants whose birth weights are between 1,500-2,500 grams survive and do fairly well, but the very low birth weight babies (VLBW - below 1,500 grams) require long periods of intensive care and have high mortality and morbidity. Postneonatal deaths (death between twenty-eight days and eleven months of life) declined from 100/1,000 live births at the turn of the century to 50/1,000 by 1950 and 3.78/1,000 live births in 1984. In 1984, the infants below 2,500 grams, which constituted 6.7 percent of all births, contributed two-thirds of all deaths, and the VLBW group, 1.15 percent of all births, accounted for half of neonatal deaths. The decline in infant mortality rate since 1960 is due mainly to a decrease in neonatal mortality (infants dying between zero and twenty-seven days of life). The task force on infant mortality of the American Academy of Pediatrics has stated that, "Although this decline is gratifying and should not be minimized, several factors point to the need for additional efforts: continued disparities in the mortality rates among the black and white populations; a recent slowing in the rate of decline in infant mortality; a possible recent increase in postneonatal mortality; etc."

In FY 1985, two new Perinatal Emphasis Research Centers (PERCs) focusing on Intrauterine Growth Retardation were funded. Some of their accomplishments are presented in the section on PERCs (page 19).

Other investigators are addressing other issues of importance to the LBW infants. The long-term influence on mortality and morbidity of low birth weight is being analyzed in British Columbia where data exists on 1.2 million individuals born between 1946 and 1981. The investigators are using record linkage techniques updating birth, mortality, and health files. In a first step, they have defined birth weight by gestational age curves for the last 8-10 weeks of gestation. The curve is identical in most groups, but the ones for East Indians, Chinese, and Japanese fall below the Caucasian-Native American curve. Therefore, it appears that the differences in birthweight between ethnic groups are established early in gestation and are unlikely to be influenced by nutritional or other factors occurring in the third trimester.

Caloric deprivation does reduce growth rate in postnatal animals, but the responsible mechanism has not been clarified. An interesting study examined two important parameters: rates of protein synthesis and degradation in muscle tissues of suckling rats. Increased protein degradation was found to play the major role under these experimental conditions.

Studies have demonstrated in the past that non-nutritive sucking (NNS) during gavage feeding improves weight gain in premature infants. However, new data obtained in a careful study where nutrient intake was controlled showed no apparent effect of NNS on growth outcome in very low birth weight infants.

> "Watch for signs of resuscitation, namely, improvement in the color, in movements, in cardiac pulsation — Never be content until the child breathes regularly, and appears to be continually improving."
>
> Francis Henry Champneys
> American Journal of Medicine Sciences, January 1886

Significant advances have been made in the understanding of Respiratory DistressSyndrome (RDS) and safe and efficacious, preventive and therapeutic approaches are being evaluated. The total NIH program is shared by the Lung Division of the National Heart, Lung, and Blood Institute, and the NICHD.

RDS is still a major health problem, occurring in fourteen to sixty percent of premature deliveries. Studies are progressing to define the molecular mechanisms involved in the biosynthesis of surfactant in order to help in the development of a rational approach to the treatment of RDS. A team of researchers have demonstrated that the developmental increase in surfactant biosynthesis in the Type II cells is promoted by the increase in intracellular cytidine monophosphate and the declining availability of myo-inositol. An interesting aspect of this research is the role of platelet-activating factor (PAF) in human fetal lung maturation. In an in vitro system, there was a reciprocal relationship between PAF and glycogen content as the lung tissue matured. This finding suggests that PAF may mediate the onset of glycogenolysis in fetal lung tissue, and glycogen degradation may serve as the carbon and energy source for the increased synthesis of the phospholipids needed for surfactant synthesis.

Somatomedin C (SmC or insulin-like growth factor I) and other growth factors influence the growth and differentiation of the fetal lung. Data suggest that a decline in SmC production by the fetal lung may be correlated with the initiation of fetal lung Type II cell differentiation. Infants of diabetic mothers are known to have a higher incidence of RDS. Preliminary studies provide a possible explanation for this observation, i.e., fetal hyper-insulinemia may cause the production of a surfactant deficient in the major apoprotein.

Another investigator is testing whether corticosteroids and thyroid hormones have functional effects on the lung that can be related to change in the permeability of epithelium and endothelium, which would result in important functional changes in lung structure. Corticosteroid therapy was shown to have complex, contradictory effects on protein leak (PL), increasing PL from the vascular space to the lung interstitium and airway and decreasing it from the alveolar epithelium to the interstitium and vascular space.

> "The bacterial origin of disease is intimately connected with preventive medicine . . . . just awakening to the dawn of a great revolution in medicine, and in this revolution bacteriology and preventive medicine will play a most important part."
>
> Medicine in 1936
> JAMA, p. 127, July 31, 1886

The newborn infant is susceptible to many infections. A significant objective in neonatology is to develop improved methods for their early diagnosis, prevention, and treatment. Neonatal infections have a wide clinical spectrum ranging from inapparent disease to sepsis which is rapidly progressive and carries a significant mortality rate.

Group B streptococci are a major cause of serious infections in human newborn infants. Studies are underway towards the identification of mothers and infants at risk for Group B streptococcal (GBS) disease. In an experimental model, it was shown that the ratio of mean concentrations of cord to maternal antibody to a specific GBS serotype increases with gestational age providing an overall view of the degree of placental passage. Further, studies with newly developed sensitive quantitative assays for antibodies are aimed at finding the critical protective level of antibody to any of the serotypes to GBS. This, in turn, will permit the evaluation of the efficacy of GBS vaccines and the development of immune serum globulin if, and when, active immunization is not possible.

Herpes simplex virus (HSV) infection in the newborn results from exposure to the virus in the maternal genital tract during delivery. In order to determine if cultures in late gestation of women with a history of HSV infection predict asymptomatic shedding of the virus at delivery, 414 women were examined. In this carefully planned, multicenter study, it was demonstrated that antepartum maternal cultures do not predict the infant's risk of exposure to HSV at delivery. Furthermore, two treatments for neonates with HSV infection were evaluated in a double-blind, controlled investigation. Both vidarabine and acyclovir produced no significant laboratory or clinical adverse effects, and both were found to be equivalent therapy in terms of neonatal mortality and morbidity.

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One of the members of the human herpes virus family, cytomegalovirus (CMV), causes congenital and perinatal infections. Disease occurs more frequently and is more severe with fetal infection and in premature infants with transfusion - acquired infection. A study involving 16,218 pregnant women concluded that primary CMV infection during pregnancy poses a 30 to 40 percent risk of intrauterine transmission and that adverse effects for the infant are more likely when infection takes place during the first half of gestation. Congenital CMV infection, which occurs in about 1% of live births, is asymptomatic in 90% of cases. Hearing impairment is observed in 15% of asymptomatic children and the remainder were found not to be at increased risk of mental impairment.

> "Does our present knowledge support the view that medicines act during definite periods; that is, can we rely on a given dose of a drug influencing the organ in which it acts for the same space of time in different individuals, or on the same individual at different times?"
>
> D. J. Leech, M.D.
> British Medical Journal, November 28, 1885

Many medications are used in the treatment of sick infants. The extent of drug uses in two neonatal intensive care nurseries was documented over a period of seven years, showing that the median number administered to patients was six, and that the use of some drugs has remained constant whereas for other drugs substantial changes were observed, e.g., decreased use of some antibiotics and digoxin and an increased use of morphine and dopamine. Twelve percent of NICU patients received morphine; for older children the rate of use varied with age, and so did the indications for the drug. In addition, data suggest that the routine use of heparin in NICUs (to maintain the patency of vascular catheters) is associated with a four-fold increase in the risk of intraventricular hemorrhage. Concurrently, it has been documented that very sick infants are exposed to various pharmaceutical additives causing serious and in some cases fatal reactions. This drug surveillance program is providing a needed overview of drug usage and effects in a vulnerable and immature population.

The cytochrome P-450-dependent system plays an important role in the biotransformation of drugs. Ongoing studies are aimed at understanding the relationship between the ontogeny of the isozymes of this system and age-related changes in the metabolism of foreign compounds. Four isozymes have already been isolated during the perinatal period and plans are under way to define differences in the expression of members of the P-450 gene family with age and tissue, and in response to inducing agents.

The use of theophylline (T) is recommended for the treatment of infants presenting with idiopathic apnea of prematurity. The central effect of T is stimulation of breathing and consequent maintenance of adequate arterial oxygen concentration. In adult humans, T causes a decrease in cerebral blood flow. Studies of preterm infants before and after T administration using nuclear magnetic resonance (NMR) showed that those with apneic spells may represent more unstable babies. The state of brain tissue oxygenation can be studied in vivo with NMR spectroscopy. In an appropriate animal model, continuously it was shown that cortex oxygenation declined rapidly during apnea and the NMR data suggest that bioenergetic reserve in brain tissues is limited and can be depleted quickly in the newborn.

An ongoing study is examining various aspects of the metabolism of steroids and xenobiotics by the placenta. It has been shown previously in rodents that exposure to polyaromatic compounds during pregnancy results in fetotoxicity and that they cause alterations in the activity of an important group of oxidative and reductive enzymes in the placenta. An appropriate steroid hormone balance is needed not only for the maintenance of pregnancy, but also to ensure fetal growth and survival. In studying the biotransformation of benzopyrene (BP), it was shown that the vascular labyrinth zone of placenta is the major site of inductions and BP metabolism. In addition, fetal rat liver and its hematopoietic cells, following maternal pretreatment at seventeen days gestation, proved to be major sites of BP bioactivation and may contribute to fetal toxicity.

The effect of antiepileptic drugs administered to patients throughout gestation is also being studied. The main goal is to elucidate the teratogenic effect of these drugs versus the teratogenic effect of the seizures themselves. The drug to be examined is Valproic acid in an epileptic non-human primate model. Pharmacokinetics of the drug during pregnancy, as well as parameters of neonatal development and social behavior, are being obtained and compared to normal pregnant monkeys as controls.

SUDDEN INFANT DEATH SYNDROME (SIDS)

> "We must dive deeper into the mysteries of Scientific Medicine and prepare to grapple with the destroyer that claims so many of earth's little ones".
>
> W.D. Haggard, M.D.
> JAMA VII, 1, July 3, 1886

Although Dr. Haggard's statement did not address the SIDS problem but the overall high mortality rate for children during the last century, his proposition that causes and treatments must be found through research is equally applicable to today's most common cause of death among youngsters between one month and one year of age. Indeed, every week more than 100 American infants die of the sudden infant death syndrome (SIDS). SIDS, formerly called crib death, is defined as the sudden death of any infant which cannot be explained by prior medical history or postmortem examination.

Between 5,000 and 6,000 babies die of SIDS annually in the United States, but SIDS occurs in all countries, cultures, and climates. Its incidence rate is estimated at 1.5 to 2.0 per 1,000 live births. Most SIDS infants die between the second and fourth month of life while asleep. The initial theory of accidental suffocation by a sleeping mother or by bedding was abandoned when research started looking into the problem. Current evidence suggests that SIDS is not caused by choking or neglect and generally is not contagious or hereditary. Although the exact etiology of SIDS remains elusive, current thinking attributes the syndrome to a combination of subtle physiological deficiencies in the infant.

With the assignment to NICHD of primary Federal responsibility for research in SIDS, a set of program objectives was developed: to expand the base of knowledge; to understand the causes and underlying mechanisms of the syndrome; to identify infants at risk for becoming victims; to explore preventive approaches; to clarify the relationship between high-risk pregnancy, high-risk infancy, and SIDS; and to elucidate the psychological impact of a sudden and unexpected infant death on parents, siblings, and the extended family.

Epidemiological Research

The NICHD Cooperative Epidemiological Study of SIDS Risk Factors compiled data on 757 singleton SIDS cases and 1,514 singleton living infants. Although the Branch has not been directly involved with the study (overseen by the Biometry Branch of the Prevention Research Program), a review and update of SIDS research would not be complete without presenting an overview of the results. Analyses of this population indicate that 54 percent of the SIDS cases were black, although only 25 percent of the births in the study centers were black. The percentage of low birth weight infants is increased among cases almost four-fold over random control infants. Several maternal factors were significantly increased for SIDS cases compared to controls. Three factors associated with the highest SIDS risk were: (1) smoking during pregnancy; (2) mother's age at first birth less than 20 years; (3) mother's education less than high school graduate. Neither alcohol use during pregnancy nor low pre-pregnancy weight (<110 lbs.) were associated with increased SIDS risk. Final results have confirmed that DPT immunization is not a significant factor in the occurrence of SIDS. An unexpected interesting result of the analysis of breast- versus bottle-feeding and SIDS risk (after adjusting for several variables: mother's age, education, income, and smoking) showed that there was a significant association between the lack of breast-feeding and SIDS. A special analysis on this same population demonstrated that almost all "apnea" in the newborn nursery occurred among preterm infants and that there were no differences in the rate between SIDS cases and the birthweight and race-matched control infants. More SIDS cases experienced prenatal and postnatal growth retardation than control infants.

Currently, a new study is reviewing records from the National Collaborative Perinatal Study which involved approximately 60,000 gravida and their offspring. The plan is to examine the cohort for risk factors: demographics, physical features of the mother, history of last prior pregnancy, disease

states, condition of pregnancy, labor, delivery, intrauterine growth, neonatal diagnosis, and other variables. Concurrently, they will carry out a case control study where each of the 125 known SIDS victims will be compared to two control groups: the first one will include eight controls per case matched on risk factors known to be related to SIDS; the second one will match non-SIDS deaths with controls selected on similar criteria. It is expected that a more complete picture of the SIDS victim will be forthcoming, providing clues for future studies.

Biomedical Research

SIDS biomedical research includes studies involving both infants at risk and SIDS victims, as well as experimental animals whose early development is similar to that in humans.

An area of intense investigation by several research teams addresses basic physiologic issues of the respiratory function in young infants. Premature infants have an increased frequency of apnea episodes and understanding their cause, effect, and consequences will be helpful in clarifying their possible relationship to SIDS. A study examined breathing patterns in premature infants which appear to be profoundly modulated by sleep state, with a shortening of expiratory duration during quiet and not during active sleep. This pattern may adversely affect gas exchange in these infants which could be partially caused by immaturity in the control and mechanics of the respiratory muscles. The interaction of central excitatory and inhibitory influences on the respiratory centers may have important implications for both prematures and newborns with apnea and infants at risk for SIDS. Using an experimental animal, it was shown that, during hypoxia, there is an increased pulmonary excretion of CO_2, suggesting that brainstem respiratory alkalosis (change in the pH of the brainstem environment) could be the cause of hypoventilation in newborns under this condition. Preliminary measurements, carried out with a novel and sophisticated technique, showed that pH of brainstem extracellular fluid does indeed increase transiently, followed by a mild decrease or acidosis. Other studies have examined the effect of postfeeding regurgitation on the breathing pattern of infants with histories of prolonged apnea. It was shown that it was a significant predisposing factor for short and prolonged mixed or obstructive type of apnea. As other studies have failed to show this association, it is conjectured that apnea may occur only when gastric material reaches specific receptors present in the upper airway (larynx). In experimental animals, the stimulation of these receptors does cause apnea and swallowing. It is speculated that in infants some regurgitating episodes do not cause apnea, as the receptors may be protected by mechanisms such as laryngeal closure or coordinated swallowing. The latter was observed in premature infants, where swallows were more common during episodes of apnea, specifically of the mixed or obstructive types.

New sophisticated techniques are being developed to study the role of brainstem respiratory-related neurons in modulating respiratory patterns. These studies, carried out in adult cats, examine the effect of various stimuli applied to the upper airways mucosa. Some common stimulus such as

distilled water and smoke were found to be inadequate as the receptor units adapted rapidly and failed to respond. The use of a stronger stimulus, a small brush, produced a greater response in individual units. This preliminary finding is a new and interesting approach to an important study.

Identify infants at risk for SIDS has been an important aim of research. The question has been raised as to whether the analysis of oscillatory patterns in respiration and heart rate can define these infants. It has been shown that oscillatory patterns do indeed underlie apnea and hypoventilatory events and may be more appropriate to examine than just tabulating the number of apneas or the percentage of time occupied by apneic episodes over the day. The technique for these studies has been refined by determining the effect of a face mask on breathing patterns and apnea. Although the presence of a mask changed the incidence of the recognized patterns, it did not modify the observed relationship between patterns and apneas. Coded tapes of 24-hours undocumented home recordings of cardiorespiratory function obtained on a large number of infants in London are available to the investigator as well as those of twenty-two infants who subsequently died of SIDS.

Ongoing studies have led to new insights on the relationship between endorphins (endogenous opioids) metabolism, the diversity in the physiologic role of the naturally occurring opiate system, cardiorespiratory control and state of consciousness or sleep. It was determined in puppies that ventilatory response to hypoxia depends on age and sleep state, with a more mature response in rapid eye movement (REM) than in quiet sleep. Endorphins were shown to be released in the central nervous system when animals were exposed to severe hypoxia. It was also shown that opioids cause a slowing down in heart rate and hypoventilation by different mechanisms.

A grant awarded through the small business innovation research program (SBIR), utilizing an existing automated cry analysis system, is studying its potential use for an early identification of infants at risk for SIDS. Under another SBIR grant, a motion-sensitive apnea monitor has been developed and a prototype built and tested in a clinical unit. It was shown to be more sensitive and able to detect apneic periods with greater consistency than the mattress-type monitor.

A project is under way to examine the role of the brainstem in the etiology of SIDS. The study involves an existing collection of brainstems of infants who died of SIDS. The objective is to determine if SIDS can be correlated with changes in the cellular make-up of the brainstem. Although qualitative changes in cells are not documented, it is thought that quantitative changes in specific cell types exist and could be detected by a morphometric analysis of a large data set.

During FY'86, a Request for Applications (RFA) entitled "The Pathogenesis of Sudden Infant Death Syndrome" was issued. The RFA centered on questions regarding the pathogenesis of SIDS in the context of the role of the brainstem and other CNS centers in the control of vital functions. Published research goals highlighted the need for studies on the neurobiology and neurobehavioral aspects of infants who are considered at risk, with the potential use of new and highly sophisticated technology. In addition, the RFA stressed the possibility of examining the role of circadian rhythms endogenously generated in infants at risk. The response to the RFA from the research community was outstanding and the proposals encompassed recognized areas for research as well as novel ideas to be explored. In issuing this RFA, the Institute hoped to stimulate investigators, not in the SIDS field, to consider the possibility of applying their expertise to this important question. This was accomplished and eight proposals are being funded. One will examine the development of sleep-state organization in infants, three will address various aspects of cardiorespiratory function and arousal, two will look at the potential involvement in respiratory control of various types of central nervous system receptors, one will investigate the possible role of an inherited lipid disorder in infant death, and one will study the developmental control of muscles involved in respiratory function.

The use of home apnea monitors for infants was the subject of a Consensus Development Conference held at NIH in September 1986. An important conclusion reached by the panel of experts who participated was that home monitoring is medically indicated for certain groups of infants at high risk for sudden death (infants who had an acute episode requiring resuscitation, siblings of two or more SIDS victims), but not recommended for normal or asymptomatic preterm infants.

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

> " . . . the discovery of specific micro-organism as the cause of a disease, places it in the list of infectious diseases, although it may not have been considered as belonging to the class."
>
> Medicine in 1936
> JAMA, p. 129, July 31, 1886

The AIDS epidemic in the United States continues to spread. The Public Health Service projection for the year 1990 forecasts 270,000 cases of AIDS in the United States, an eventuality of staggering cost in both human and economic terms. As noted by the Centers for Disease Control, the number of women infected by human immunodeficiency virus (HIV) is increasing. The primary route of HIV infection in children is from infected mother to child and the NICHD has undertaken a number of research projects related to human immunodeficiency virus infection in infants, children, and mothers. The responsibility for these studies is shared by the Pregnancy and Perinatology Branch and the Epidemiology Branch of the Prevention Research Program. The current studies are focused upon: (1) a definition of the rate and determinants of the perinatal transmission of HIV infection from infected

mothers to their children. This multicenter study is being conducted in three hospitals in New York City. (2) a description of the full spectrum (physical, neurological, developmental) of HIV infection in children who acquire their disease as a result of congenital infection. (3) a complete profile of the immunologic changes which occur in HIV seropositive and seronegative mother-infant pairs (prepartum in the mother and postpartum in the mother and infant). (4) a multicenter study of the natural history of HIV infection in hemophiliac children who were exposed to the virus via contaminated clotting factor replacement products. (5) a seroprevalence survey of HIV in 30,000 births in the northeastern United States (outside of the major AIDS epicenters) in order to determine the prevalence of HIV infection in women of reproductive age in areas of presumed low prevalence. (6) a prospective, blinded study of the so-called AIDS embryopathy/fetopathy syndrome in order to validate or refute the existence of this entity. (7) a double-blind placebo controlled randomized clinical trial of the efficacy of intravenous gamma globulin in infants and children with symptomatic HIV disease.

In the first study, we have enrolled almost 100 women in New York City who are at high-risk for HIV infection. So far, 45 have had their babies. Of these women, 19 were seropositive for HIV. To date, 2 infants have AIDS (one is dead), and 4 are highly symptomatic for HIV disease. In the second study, we have preliminary results suggesting that the neurological systems of infants exposed to the virus in utero or intrapartum are affected very early in life. In fact, with careful examination, developmental delay may be one of the earliest signs of HIV infection in victims of perinatal transmission of this disease.

PERINATAL EMPHASIS RESEARCH CENTERS (PERC'S)

The program was started in 1977 under the name of Major Research Programs (MRP), and the official designation was changed to PERC in 1984. The PERCs are intended to promote and support multidisciplinary research efforts in areas where (a) knowledge gaps are not being sufficiently addressed by ongoing research, or (b) there are needs to stimulate and intensify efforts in promising research areas. Two active PERCs are in the area of "Diabetic Pregnancy", one is in "Hypoxia and Maternal Smoking", one addresses the issue of "Prematurity and Initiation of Labor", and the newest two centers support studies on "Intrauterine Growth Retardation". Another PERC in Diabetic Pregnancy was just completed. PERC investigators and NICHD staff meet every year to discuss goals, scientific accomplishments, and directions for future research.

Diabetic Pregnancy

Untreated diabetes mellitus is incompatible with successful outcome of pregnancy. As treatment of diabetes has improved, pregnancy outcome has improved, and presently maternal mortality is similar for diabetic and nondiabetic women. However, maternal morbidity continues to be higher in diabetics. Fetal mortality has been reduced, but not to the level in the general population. Increased incidences of congenital anomalies, macrosomia, late intrauterine death, and respiratory distress syndrome (RDS) remain a

significant problem. Pregnancy per se has a diabetogenic effect, and some women develop abnormalities of carbohydrate metabolism known as gestational diabetes mellitus (GDM).

Reviewing the clinical data obtained in the follow-up of 138 patients with GDM, a profile emerged indicating that patients who needed insulin, in addition to their dietary regimen were, in general, older than 25 years, and delivered infants with a higher birthweight than those who could be controlled by diet alone. Obese patients with GDM had an even higher risk for neonatal macrosomia. This finding underlines the need for rigorous glucose regulation during the antepartum period. Furthermore, intrapartum glucose administration to the mother should be limited and requires careful monitoring of the fetus as it produces a significant decrease in neonatal glucose concentration and changes in acid-base relationship.

Animal models (rhesus monkey, rat, lamb) have been developed to produce chronic in-utero hyperinsulinemia resulting in fetal overgrowth (similar to human fetal macrosomia). The observed fetal overgrowth is not a transient phenomenon, and at 15 days of age, rat pups exhibited an elevated fatty acid content in both liver and muscles. Accelerated lipogenesis cannot explain this observation as the rate of fatty acid synthesis remained unchanged when compared to control pups. Studies in another animal model to produce in-utero growth retarded rats examined the effect of nutrition on the growth pattern during the first week of life. Postnatal feeding did not affect the severely growth retarded pups, and the decrease in tissues' fatty acid content and synthesis was found to be proportional to the reduction in bodyweight. Preliminary results of studies examining behavioral development of rhesus monkeys made hypoglycemic during their newborn period as a consequence of fetal hyperinsulinemia show some deficits when compared to normal controls. This observation in young animals persists in the few that have reached adolescence (4 years old).

It has been demonstrated in the adult that the response to glucose infusion is a decrease in glucose production. In the first few days after birth the newborn shows a persistent neonatal glucose production in response to exogenous glucose. Studies carried out in infants throughout the neonatal period demonstrate a transitional control of glucose kinetics which may partially account for the frequency of hyperglycemia noted clinically. Previous studies showed that rat pups treated with insulin in utero exhibited accelerated growth which persisted for two weeks. Further studies have shown that this accelerated growth persisted to 12 weeks of age. Although experimental and control animals had similar body weights, the insulin-treated pups responded with higher plasma glucose to an oral challenge test. This response may indicate that fetal hyperinsulinemia and macrosomia alter pancreatic beta cell development resulting in abnormal glucose homeostasis and accelerated growth.

Metabolic studies in humans showed that, at term, the fetus is totally dependent on the mother for glucose but is able to produce alanine endogenously, a major glucogenic amino acid. It was also shown that there is an increase in maternal protein turnover in both diabetic and non-diabetic

patients. Matabolic studies in lean, mildly obese, and massively obese women did not uncover major differences, even though the latter group had what is usually considered inadequate pregnancy weight gain.

The consequences of the aberrant intrauterine environment in diabetes and intrauterine growth retardation (IUGR) upon neonatal metabolic adaptation were examined. The data showed that as in adults, the endogenous glucose production in the newborn is regulated by plasma glucose, and neither prematurity nor IUGR exert any significant effect on this regulation. Recycling of glucose carbon accounts for about one-third of glucose production indicating active gluconeogenesis in the fasting newborn. Oxidation of plasma glucose represents only 80 percent of total carbohydrate oxidation suggesting that there is oxidation of local tissue glycogen. The measured rate of glucose oxidation seems insufficient to supply cerebral metabolic requirements, and other fuels may be important for cerebral metabolism in the fasting human newborn. Lactate turnover is higher than in adults reflecting increased glycolysis and higher oxygen consumption. When the newborns were either IUGR or infants of a diabetic mother, similar results were obtained.

Perinatal morbidity and mortality is markedly increased in infants born to insulin-dependent diabetic women (IDD). This increase includes macrosomia with its attendant birth trauma. Fetuses of IDD women are known to have an altered growth pattern in utero. Data obtained by a team of researchers reveal that sonographic growth patterns in IDD pregnancies differ from the standard charts that have been constructed for the normal population. They begin to show accelerated growth at 24 weeks gestation and the difference persists to term. Also, studies have shown a high incidence of neonatal polycythemia in infants of diabetic mothers which suggests an increased rate of erythropoiesis.

Electronic monitoring of heart rate and movement has allowed studies examining cyclic motility of fetuses which is present as early as 21-24 weeks of gestation. Normal fetuses exhibit active and quiet periods which become longer with age. This feature was not observed in the fetus of the insulin-controlled diabetic patient, suggesting a delay in maturation in fetal cycles.

In humans, efforts are being directed to clarify the pathophysiologic mechanisms of bone demineralization in infants. Preliminary clinical studies are showing that in diabetic pregnancies there is decreased magnesium concentration in the amniotic fluid. This deficient state may contribute to neonatal hypocalcemia. The mineral content of bone in infants of diabetic mothers was found to correlate with the mean glucose concentration in capillary blood during the first trimester of pregnancy and with the mineral content of maternal bones. In assessing infant vitamin D status it was found that race, age, season, and diet exert significant effects on vitamin D metabolites and therefore, these factors should be considered for each individual patient.

An important research project has continued to develop an implantable open loop insulin infusion system with peritoneal access for treatment of insulin dependent diabetes mellitus. The system delivers insulin in a preprogrammed fashion and the patient can adjust the insulin delivery according to periodic

discrete blood glucose measurement and anticipated caloric intake. The system has been reduced in size and weight and all components are housed in a single case. There have been several relatively short-term implantations in humans, showing that intraperitoneal administration of insulin is feasible. Two-way telemetry allows communication with the implant so that it can be programmed and reprogrammed at will. At the same time, its performance can be checked with regard to delivery rate, cumulative insulin delivered, remaining amount of insulin, battery status, and pump motion. The importance of being able to restore and maintain normal glycemia must be emphasized as it appears to prevent or even reverse early microvascular complications in diabetic patients.

Hypoxia

Adverse antenatal events, prior to the onset of labor, may cause developmental handicaps. Decreased availability of oxygen (hypoxemia) to fetal tissues is such an event and a reliable marker to assess its occurrence is needed. The measurement of neuropeptides (vasopressin) in amniotic fluid may be such marker. Successive studies have shown that decreased oxygenation results in an increase in the secretion of vasopressin (antidiuretic hormone released by the posterior lobe of the pituitary). Vasopressin is then promptly excreted in the fetal urine and can be measured in amniotic fluid. Concurrent studies have also determined that anterior lobe hormones are stimulated by hypoxia in the human fetus and all play a role in the fetal adaptation to a decrease in oxygenation. Although fetal osmolality is a reflection of maternal status, the fetus plays a role in a finer tuning of its homeostasis. Indeed, a moderate release of vasopressin contributes to water conservation, and a greater release (in response to hypoxia) contributes to the maintenance of blood pressure. Studies in sheep have shown that the ability appropriately to respond to hyperosmolality is present early in the third trimester, with a tendency to mature towards term, and no changes occurring during the first postnatal week. The response to hypoxia changes with age when examined in fetuses, neonates, and 5-7 day old lambs. Some changes are caused in part by maturation of the autonomic nervous system but other factors, such as transition from fetal to neonatal circulation and the establishment of ventilation, are likely contributors.

Chronic maternal hypovolemia produced in an animal model affects the fetus and can lead to hypoxemia. Some of the recorded changes were an increase in fetal plasma renin activity, vasopressin, and catecholamines. Various forms of stress including acute hypoxia were shown to be associated with the systemic release of beta endorphin and vasopressin. This response was found to be present in fetal life and maturing over time. Experimental data suggest that vasopressin participates in both the stimulation and feedback inhibition of anterior pituitary in a stressed newborn. Another regulator of fetal pituitary and adrenal functions seems to be corticotropin releasing factor (CRF) in the peripheral circulation of the fetus. Experimental findings indicate that there may be a placental source for CRF. The investigators are trying to determine the potential utility of these measurements to be used as indices of placental function. Human studies examining breathing of the fetus of smoking mothers have indicated significant differences in the variability of fetal breathing by epoch analysis when compared to non-smoking conditions.

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Prematurity and Initiation of Parturition

Prematurity is associated with more than 60 percent of all infant deaths and increased morbidity in the survivors. One center is actively pursuing studies detailing the biochemical events that accompany the onset of labor. A greater understanding of these mechanisms will facilitate the design of new and effective strategies to prevent premature labor. In the past, studies have shown that a precursor of prostaglandins (arachidonic acid) is mobilized from fetal membranes during human parturition and that platelet-activating factor (PAF) is undetectable in human amniotic fluid before but present after labor. It was demonstrated that PAF can be synthesized in amnion tissue and that this process is stimulated by calcium. This finding provides further support that ionized calcium plays a central role in the initiation and propagation of the biochemical events of human labor.

Studies are examining the regulation and metabolism of arachidonic acid in amnion, chorion, and decidua. Recent experiments suggest that ethanolamine plasmalogen, found in amnion tissue, serves as a source of arachidonic acid and also inhibits the complete hydrolysis of glycerophospholipids by serving as an endogenous inhibitor of lysophospholipase. Following the characterization of a calcium ion-dependent phospholipase A_2 activity in amnion tissue, further studies are suggesting another phospholipase A_2 activity in amnion tissue that is calcium ion-independent and may be responsible for the formation of platelet activating factor. Another area of ongoing studies is that of the regulation of prostaglandins during parturition. Onset of labor in infected patients appears to be induced by a host-related product secreted by monocytes in response to parentaral endotoxin which is capable of inducing prostaglandin release from amnion. Therefore, onset of labor in these cases may not be caused by a direct bacterial toxic effect. Studies are progressing to characterize a substance found in human fetal and adult urine that acts in a tissue-specific manner to stimulate prostaglandin synthesis in human amnion cells maintained in culture. Findings to date suggest that this substance in human urine is a growth factor of renal origin that may be of importance not only in the initiation of parturition but also in fetal growth and maturation.

Intrauterine Growth Retardation

Two centers are actively engaged in studies addressing this important issue. One study has the objective to extend the current understanding of normal and abnormal fetal growth and to determine how the fetus allocates limited exogenous nutrients under conditions of spontaneous and experimentally induced IUGR. A guinea pig model has been established and appropriate techniques to handle fetal tissues are being developed. Preliminary data suggest that spontaneous growth retardation can be described as exponential growth along a curve approximately 20% reduced from the average. Another subproject studies the effects of the restriction of glucose supply (major energy substrate) and of a decrease of fetal insulin concentration (major fetal anabolic hormone) on fetal and placental growth and metabolism in the sheep model. Two methods to produce sustained hypoglycemia are being tested and evaluated: use of phloridzin and chronic insulin infusions in non-pregnant animals which will

then be applied to the pregnant sheep. Fetal hypoinsulinemia induced by administration of streptozotocin showed that fetal hyperglycemia resulted from a decrease of pancreatic insulin content and secretion. Insulinopenia resulted in hyperglycemia by apparent increased production and perhaps by decreased utilization, resulting in decreased umbilical glucose uptake while glucose oxidation also decreased. Thus, maintenance of oxygen consumption appeared to be the result of a combination of increased endogenous glucose production and oxidation of other substrates. Placental glucose consumption and transport was not affected by streptozotocin administration to the fetus. In the presence of insulinopenia, but near normal glucose utilization, amino acid turnover was found to be increased resulting in elevated fetal amino acid concentrations.

In humans, the clinical management of IUGR relies upon the best timing of delivery to avoid severe fetal distress with its sequelae of neonatal complications. Umbilical cord blood sampling in pregnancies complicated by IUGR (diagnosed by ultrasound measurements) obtained at gestational age 31-36 weeks, were analyzed for lactate concentration and respiratory gases. Results were compared to those of normal term fetuses whose samples were obtained from the umbilical cord at the time of elective, repeat cesarean sections. These preliminary studies showed that high blood levels of lactate can precede any significant increase in acidosis and, therefore, may be used as an indicator of fetal jeopardy when antepartum fetal heart rate testing is normal.

The availability of techniques for sampling fetal cord blood in early pregnancy for prenatal diagnosis has permitted the study of the metabolic environment of the undisturbed mid-gestation human fetus. Both the pO_2 and O_2 saturation were found to be higher and the pCO_2 lower in the mid-term fetus than at the time of Cesarean deliveries. It is possible that these differences are not due to gestational age differences, reflecting the fact that data at term are collected when the mother is under anesthesia and surgical stress. Concurrent studies examined maternal and fetal carbohydrate metabolisms at the time of delivery and during pregnancy. At 20 weeks it was demonstrated that the maternal-fetal gradient is much smaller than later in pregnancy. At low maternal glucose concentrations, the gradient is reversed with fetal glucose concentration higher than in the mother.

Investigators are also examining the role of epidermal growth factor (EGF) on subsequent postnatal growth and differentiation. Preliminary experiments have shown that injecting neonatal mice with EGF produces growth retardation and the effect is greater in the period immediately following birth. They have also uncovered a new syndrome of EGF induced skin inflammation accompanied by a diminution of suckling behavior.

COOPERATIVE AGREEMENTS

Two Requests for Cooperative Agreement Applications were issued during FY 1985 inviting proposals for multicenter cooperative clinical studies in Neonatal Intensive Care Units (NICUs) and in Maternal-Fetal Medicine Units (MFMUs). They were designed to investigate, in NICUs, the safety and efficacy of new

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treatment and management strategies used for the care of sick infants and, in MFMUs, problems in clinical obstetrics, particularly those related to prevention of low birth weight. The two networks, each one consisting of seven centers, began their activities during FY 1986 and are developing protocols to be implemented during FY 1987.

A newly awarded cooperative agreement to AMSPDC is discussed under research training (page 4).

CONTRACT PROGRAM

In 1969, the NICHD recognized a growing awareness of the potential of nonhuman primates for perinatal and developmental research. A special breeding colony was established in 1971 and continues to be supported under contract at Davis, California, which provides rhesus monkeys of known medical, reproductive, and genealogical histories to NICHD-supported investigators in the United States.

In collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), six contracts were awarded in FY 1984 (five clinical centers [NICHD] and one data management center [NIAID]) to carry out a clinical trial, entitled "Prevention of Prematurity by Detection and Treatment of Gestational Genitourinary Infections: A Multicenter Randomized Controlled Clinical Trial." The objectives of these contracts are to identify specific types of maternal genitourinary infection which are significantly associated with preterm labor and birth, and to test whether appropriate antimicrobial therapy of such infections can reduce the preterm birth rate in women at risk. Slightly fewer than 9,000 patients have been enrolled since FY 1985. The study is carried out in a double blind design; results will not be available until the code is broken and results analyzed.

The Branch, in collaboration with the Mental Retardation and Development Disabilities Branch of the CRMC, NICHD, and the Division of Maternal and Child Health, Health Resources and Services Administration awarded a contract entitled "Long Term Outcomes of Very Low Birth Weight Infants" to evaluate children at ages 5 to 8 years who are survivors of a newborn intensive care unit and had a birth weight below 1,500 grams.

SMALL BUSINESS INNOVATIVE RESEARCH (SBIR) PROGRAM

The SBIR Program began in 1982 to stimulate technological innovation and use of small businesses to meet federal research and development (R/D) needs. The implementation plan proceeds in phases. Phase I has the objective of establishing the technical merit and feasibility of R/D ideas which may ultimately lead to commercial projects or services in the health area. Phase II promotes the in-depth development of proposed R/D ideas that are likely to result in commercial products or services.

Phase I Grants

An interesting project of clinical relevance has the objective of developing a tester for infant ventilators. The device will be capable of testing ventilators under physiological load conditions before being used for infant care to insure adequate performance. It is expected that the infant lung simulator will have variable compliance and resistance, and it will be tried in a hospital environment.

A novel undertaking with considerable scientific merit is trying to develop a prototype of an easily usable, nontraumatic apparatus for the accurate assessment of body volume in normal and low birth weight infants. In addition, it is planned to include a device to assess energy expenditure. The unique approach of these investigators is that of using air instead of fluids as the displacement element to measure volume.

Another project is directed at the development of an ultrasonic fetal heart rate monitoring system that should operate without interference from fetal/maternal movement. To achieve this purpose, it is planned to use broad ultrasonic beams. If successful, the system will be less sensitive to motion, will require less operator skill, and will be more useful to long-term monitoring.

Phase II Grants

One of the SBIR grants successfully completed Phase I of the proposal and began Phase II for perfecting the design and testing of an infant isolette and monitoring cradle to use in a Nuclear Magnetic Resonance (NMR) spectrometer. The ongoing clinical trials will assess the possibility of using this cradle in conjunction with NMR to predict or identify life threatening hypoxia in young infants.

Another group was able to achieve an automatic record production of fetal monitoring strips and printing the annotated reduced records. In Phase II, they will design, field test, and evaluate the system which should be clinically acceptable, and produce archival records for inclusion into the patients' charts. Ultimately, this fetal records management system will be applied to both hospital and physicians' office use.

FUTURE RESEARCH EMPHASES

High-Risk Pregnancy and Preterm Labor

Diagnostic ultrasound for fetal and placental imaging has evolved during the last decade into a major prenatal diagnostic technique. More recently, Doppler ultrasound has been used to assess human fetal hemodynamics both centrally and peripherally, and also to assess the uteroplacental circulation. Such a development is intriguing because current methods of monitoring fetal well-being have limitations. Preliminary studies have suggested the Doppler velocity waveform abnormalities may precede clinical

problems such as IUGR, and these abnormalities correlate well with neonatal morbidity. Replication of these findings is urgently needed, as well as physical and animal modeling to clarify the interpretation of velocimetry changes. Also, progress in waveform analysis and in estimating blood flow quantitatively in relevant vessels is very important to pursue. The planned workshop on Doppler Ultrasound in Maternal-Fetal Hemodynamics was held in September, 1986 and produced recommendations consistent with the above description. An RFA is planned to stimulate research on this topic.

Physical stress during pregnancy is becoming more varied, intense, and widespread as women generally become more active in sports and in the workplace. Recent studies in women exercising voluntarily at high intensity during pregnancy suggest a negative effect on gestational length and fetal growth, without increased perinatal morbidity and mortality. Further studies are needed to specify the effects and risks of intense physical activity on both mother and fetus at different stages of gestation. Follow-up studies of child growth and development can complement the perinatal aspects. Basic physiological research will also be essential to understanding the mechanism of observed effects and risks. The RFA would be issued for FY 88. One RO1 grant and a PO1 sub-project represent the only ongoing research in this area.

Currently used predictors of low birthweight are largely historical and socio-demographic, and correlate weakly with low birthweight. Availability of a biologic marker of higher reliability would facilitate early prenatal identification and intervention in a biologically high-risk population. Some studies have suggested that the expansion in plasma volume of normal pregnancy may be impaired in advance of IUGR and PIH. Newer methodologies such as mass spectroscopy and activation of stable isotopes need to be applied safely to obtain more precise measurement of plasma volume changes and correlate the latter with pregnancy outcome. Other potential predictors, such as ratios of hormones playing a role in plasma volume regulation, are also worthy of study. A research planning workshop is planned for September, 1987. In FY'88, a contract to improve and validate plasma volume measurement and other methods would be developed. Later, an RFA could stimulate research with the new methods.

The recent NICHD Consensus Conference on Diagnostic Ultrasound in Pregnancy recommended several medical indications for prenatal ultrasound, but called for additional clinical research to assess whether prenatal ultrasound screening and gestational dating improves pregnancy outcome. Published studies have been conflicting in conclusion and of low statistical power. A bi-center clinical trial is being initiated to provide data upon which general clinical recommendations can be made. The trial will span 4 years.

One of the identified priority areas of the Branch is initiation of labor. The prevention of low birth weight infants is one of the NICHD and PHS initiatives. These infants, who are at an increased risk for morbidity and/or mortality, may have been growth retarded in utero or have been bornprematurely. The clarification of the mechanisms interacting to initiate either term or premature labor is of fundamental importance if successful interventions for prevention are to be developed. An NICHD Research Planning

Workshop is planned to assess the ongoing research and current knowledge of the multiple factors responsible for initiation of labor, both term and premature, and to identify gap areas where research should be encouraged and supported. Workshop proceedings will be published.

Management of preterm labor includes the administration of oral tocolytic agents and their dosage, in many instances, is adjusted according to the patient's uterine activity recorded by an ambulatory tocodynamometer. It is proposed for FY'88 to co-sponsor a workshop with the Prevention Research Program to evaluate current experience in the use of tocodynamometry and identify appropriate studies to resolve the issues raised about the reliability and efficacy of this intervention.

Several clinical managements of conditions in maternal-fetal medicine need more rigorous evaluation in terms of relative efficacy and safety. A major barrier to performing significant clinical trials of such managements has been the low prevalence of serious adverse outcomes, such as fetal mortality. Clinical trials should be conducted in diverse populations, by different clinical researchers, but with coordinated protocols, in order that the results be generalizable. Therefore, the NICHD has established a network of seven MFMU centers, capable of cooperating in multi-center clinical trials. The centers, in collaboration with NICHD staff, will select problems to be studied, design protocols, and implement the trial with patients from the centers. Data collection and analysis will be performed by a data coordinating center which is an integral part of the network. The network is capable of carrying out several protocols simultaneously. The first protocol on management of post-term pregnancy will be initiated in FY'87. The perinatal outcomes in a group of postterm pregnancies in which induction of labor and delivery is effected will be compared with those in a randomized control group allowed to deliver spontaneously, but with careful, frequent fetal assessment until labor. A second protocol, probably on preterm rupture of membranes, will start in FY'88. Ancillary studies may also be appropriate during these trials.

Fetal Pathophysiology and Disorders of the Newborn

Over the last few years important research has brought forth new knowledge on fetal development and has opened new avenues for future investigations. One area of high priority addresses the NICHD initiative on the prevention of low birth weight in infants. Promising and rapidly expanding multifaceted studies are looking at the role of growth factors in fetal life and their relationship to intrauterine growth retardation (IUGR). These will be continued to determine if a subset of small infants reflect an aberrant expression of growth factors, abnormality in receptors or post-receptor defects. Preliminary data have shown that foreign compounds do interact with growth factor receptors and may be one possible cause of IUGR. It is planned to encourage studies in perinatal pharmacology and toxicology to acquire knowledge on the effect of drug therapy on maternal and fetal tissues and organs, the function of the placenta, and the consequences for the infant. Expansion in Perinatal Pharmacology and Toxicology will be achieved through the funding of a center to be incorporated into the PERC program. An RFA will be developed for this purpose.

The planning of a workshop on growth factors and their role in fetal growth and maturation will begin in FY'88 to identify specific interesting aspects for future research. At that time a decision will be made as to the issuance of a program announcement or an RFA highlighting the recommendations of the workshop.

The Cooperative Multicenter Network of Neonatal Intensive Care Units will begin enrolling patients for the first protocol in the current year; other protocols are at various stages of development. It is expected that there will be a continuous identification of research topics with the ensuing generation of active protocols. The purpose will be to investigate the safety and efficacy of treatments and management strategies that may be employed in the care of infants admitted to the neonatal intensive care units.

Sudden Infant Death Syndrome (SIDS)

The support of SIDS research has grown during the current fiscal year. Apnea of prematurity is a recognized problem occurring in 30 to 50 percent of infants and even 90 percent in those who are born at 28-29 weeks, or fewer, of gestational age. Further studies are needed to clarify the underlying pathogenesis. Research is currently addressing the pathophysiology of apnea but expansion is planned to evaluate the maturity of the respiratory centers. The Consensus Development Conference (held September, 1986) on the use of home monitors identified several questions which must be examined: comparison of the efficacy of Rx with teophylline or caffeine to prevent recurrence of significant apnea; determination of drug concentration in blood for effective results and lengths of treatments; development of an appropriate protocol to wean infants off the drug; and clarification of the rationale for the use of home monitors. In addition, a comparison of infants followed at home with either apnea monitors or with special care and no monitors was recommended to evaluate the outcome of these infants and to determine the indications for the use of home monitors.

Research has highlighted that SIDS victims, as a group, tend to have had more medical complications, and some victims had chronic problems of respiratory control. Under these circumstances they might be more vulnerable, specially in the event of a mild upper respiratory infection. The thought has been offered that under these circumstances some infants may not be capable of defending themselves against respiratory occlusion. An RFA is planned for FY'88 to stimulate studies examining the presence in these infants of learned behavioral mechanisms such as appropriate postural maneuvers to free their air passages as well as means of conveying their respiratory distress to others. It is expected that proposed studies will document the possible role of learning processes in facilitating such life-saving coping skills.

Acquired Immune Deficiency Syndrome (AIDS)

The Pregnancy and Perinatology Branch will continue to participate in the ongoing program and help in developing new projects addressing emerging questions in maternal and congenital AIDS. The information to be generated is vital to the delineation of successful treatments and/or prevention strategies, looking toward the day when more than ameliorative therapy is available for children and the following description of current pediatric AIDS intervention becomes obsolete:

> "Current pediatric AIDS therapy may be described as ... treatment that never ends for a disease that is never cured."
>
> James Oleske, M.D.
> March, 1987

FIGURE 1

NICHD RESEARCH PROGRAMS: THE PREGNANCY AND PERINATOLOGY BRANCH

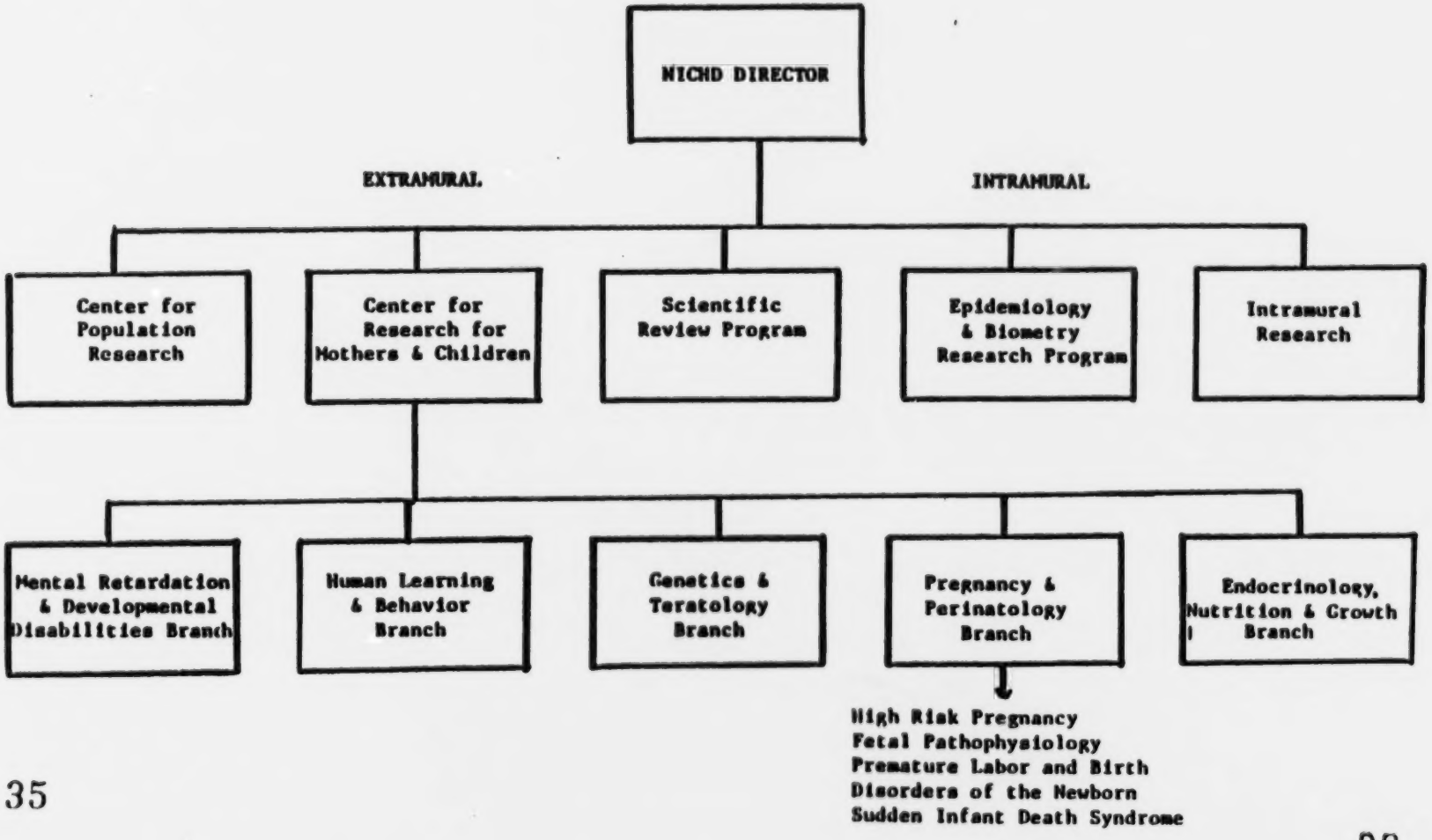
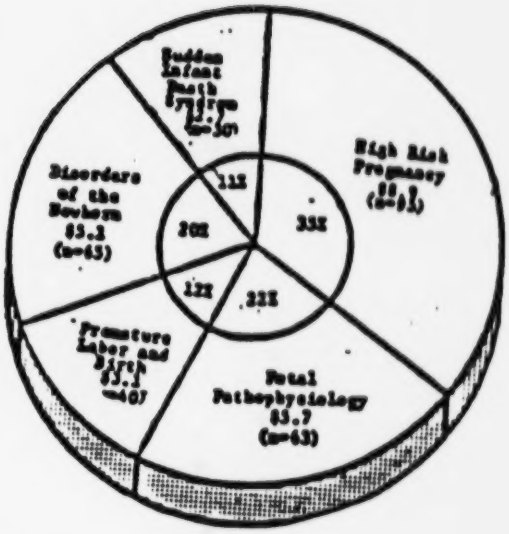


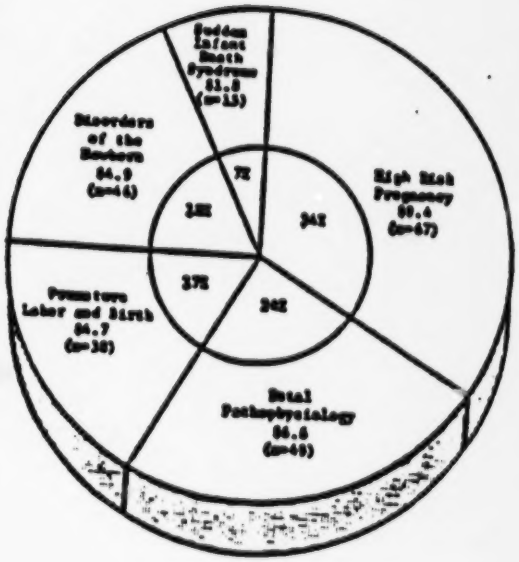
FIGURE 2.

RESEARCH GRANT AND CONTRACT FUNDS BY PROGRAM CATEGORY
FY 1980, FY 1983, AND FY 1986

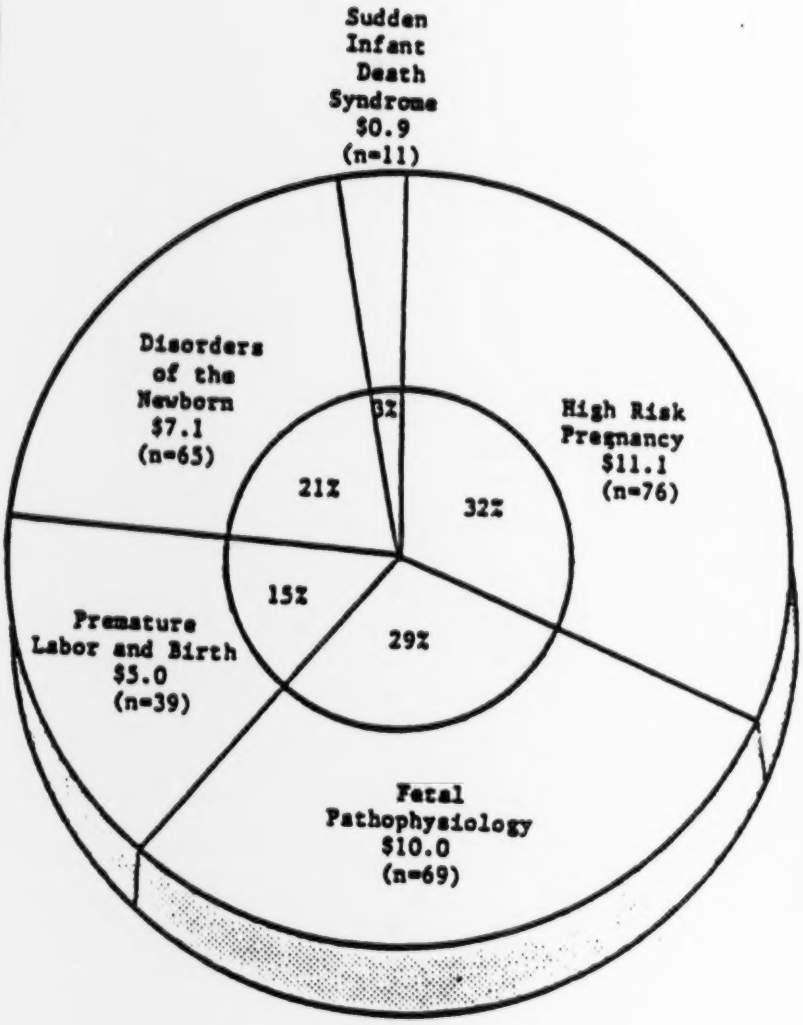
PREGNANCY AND PERINATOLOGY BRANCH



FY 1980



FY 1983



FY 1986

Funds (in millions)

FIGURE 3

PP GRANT AND CONTRACT FUNDS BY PROGRAM CATEGORY, FY 1983 AND FY 1986

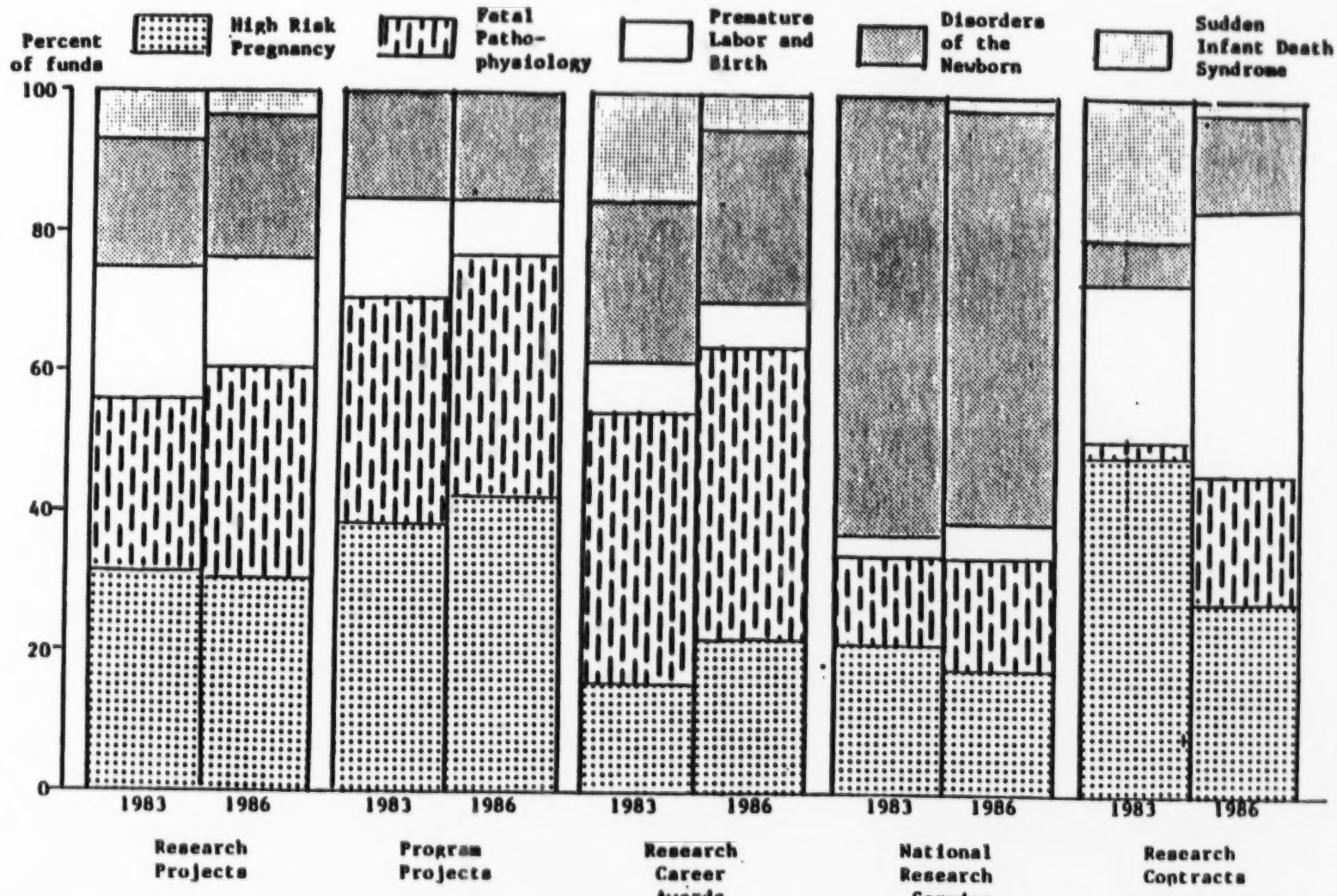
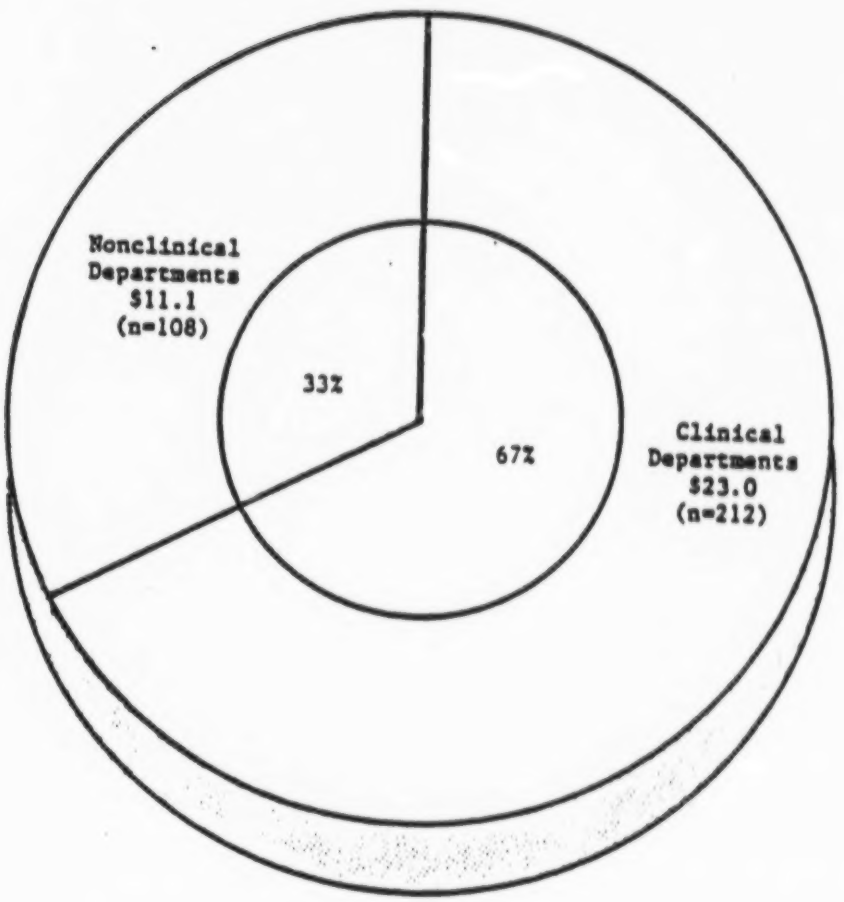


FIGURE 4.

RESEARCH GRANT AND CONTRACT FUNDS IN CLINICAL AND NONCLINICAL DEPARTMENTS, FY 1986

PREGNANCY AND PERINATOLOGY BRANCH

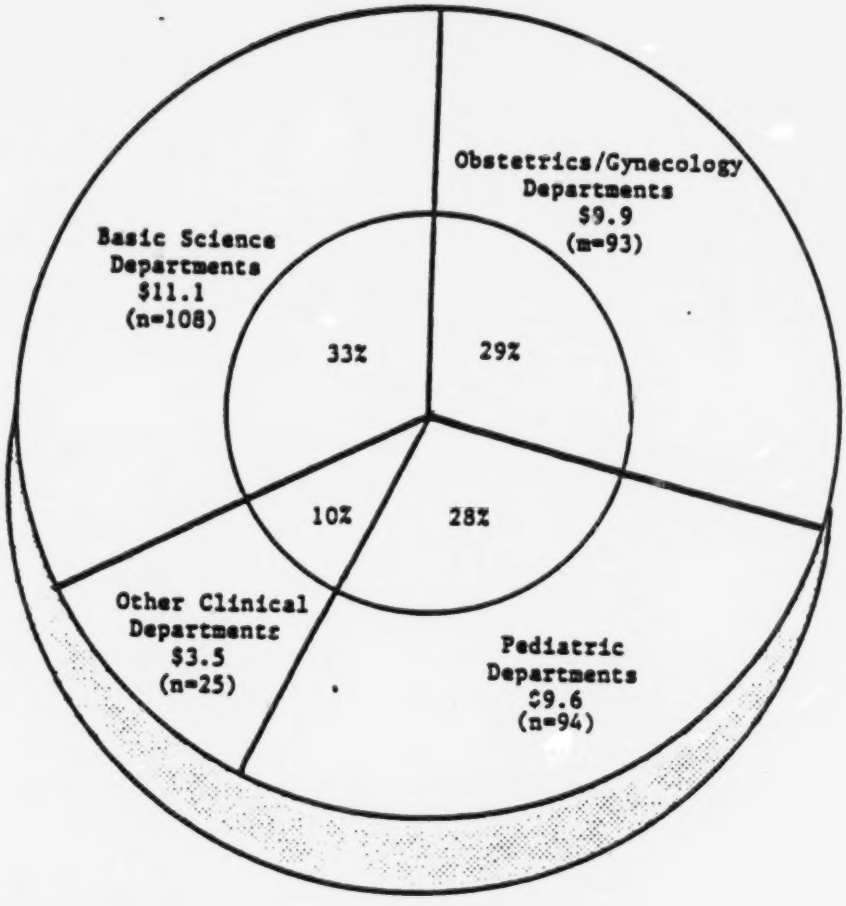


Funds (millions)

FIGURE 5.

RESEARCH GRANT AND CONTRACT FUNDS DISTRIBUTED BY DEPARTMENT, FY 1986

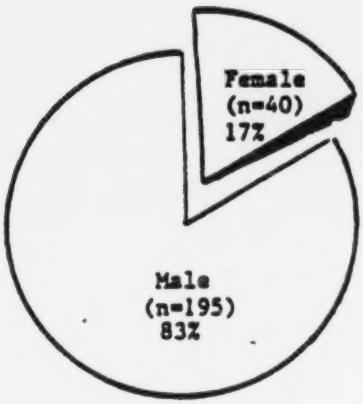
PREGNANCY AND PERINATOLOGY BRANCH



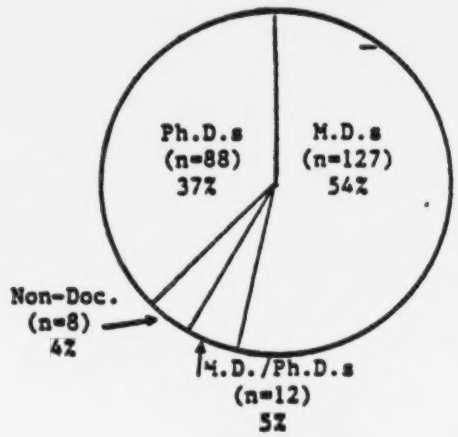
Funds (millions)

FIGURE 6

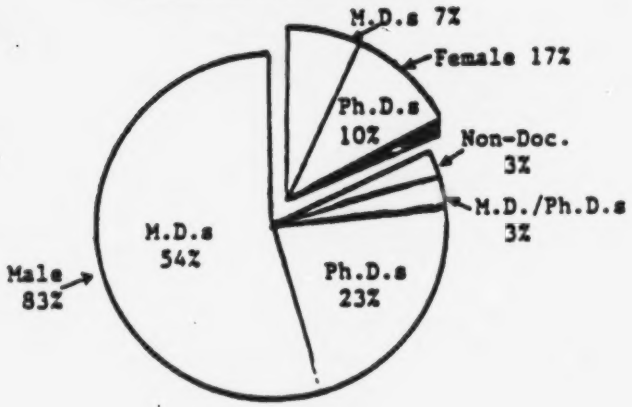
DISTRIBUTION OF PP PRINCIPAL INVESTIGATORS BY GENDER, DEGREE AND DEPARTMENT, FY 1986



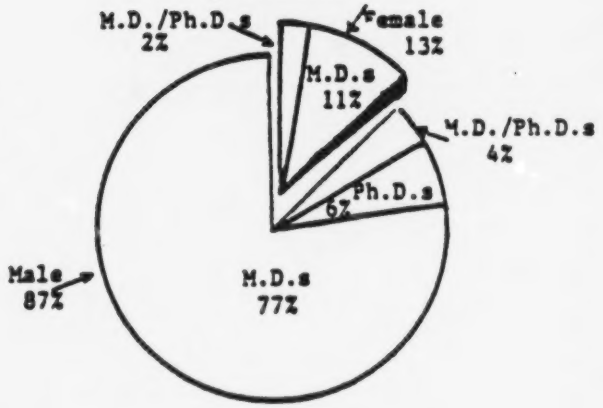
TOTAL MALE, FEMALE



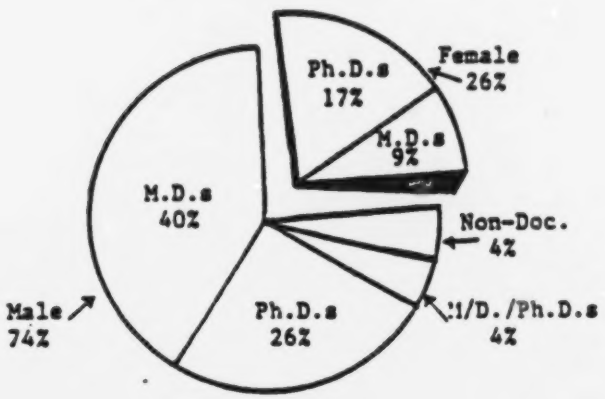
OBSTETRICS/GYNECOLOGY



PEDIATRICS



OTHER CLINICAL



BASIC SCIENCES

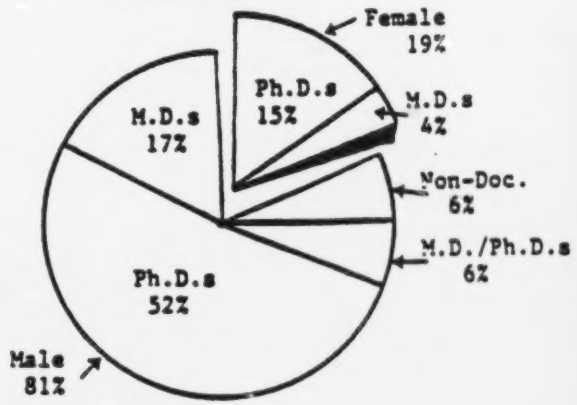


TABLE 1.

PP GRANTS AND CONTRACTS, FISCAL YEAR 1986, BY PROGRAM CATEGORY

Funds (thousands)

Program Category	Total	Research Grants				National Research Service Awards	Research Contracts
		Total Research	Research Projects (Incl.P01)	Research Centers	RCP Awards		
Total	$34,059	$29,540	$23,848	$4,632	$1,060	$1,681	$2,837
High-Risk Pregnancy	11,071	9,959	8,614	1,110	235	310	802
Fetal Pathophysiology	9,966	9,232	6,566	2,220	446	215	519
Premature Labor and Birth	5,023	3,903	3,186	651	66	65	1,055
Disorders of the Newborn	7,127	5,641	4,731	651	259	1,064	421
Sudden Infant Death Syndrome (Primary)	871	804	750	-	54	27	40

Number of Projects

Program Category	Total	Research Grants				National Research Service Awards	Research Contracts
		Total Research	Research Projects (Incl.P01)	Research Centers	RCP Awards		
Total	260	211	187	7	17	24	25
High-Risk Pregnancy	76	65	60	1	4	5	6
Fetal Pathophysiology	69	61	51	3	7	5	3
Premature Labor and Birth	39	30	28	1	1	1	8
Disorders of the Newborn	65	47	41	2	4	12	6
Sudden Infant Death Syndrome (Primary)	11	8	7	-	1	1	2

Notes: 1) The Minority Biomedical Support Grant (S06) is included in with the research projects.
2) Excludes one grant and five contracts funded from sources other than NICHD extramural funds.
3) Excludes the Scientific Evaluation Grant.

TABLE 2.

GENDER, DEGREE AND FUNDS OF PP PRINCIPAL INVESTIGATORS BY DEPARTMENT, FY 1986

Department	Total PP					Female					Male				
Type of Degree	No.	M.D.	Ph.D.	MD/PhD	Non-Doc	No.	M.D.	Ph.D.	MD/PhD	Non-Doc	No.	M.D.	Ph.D.	MD/PhD	Non-Doc
Total	235	127	88	12	8	40	17	22	1	-	195	110	66	11	8
Obstetrics/ Gynecology	61	37	20	2	2	10	4	6	-	-	51	33	14	2	2
Pediatrics	70	62	4	4	-	9	8	-	1	-	61	54	4	3	-
Other Clinical	23	11	10	1	1	6	2	4	-	-	17	9	6	1	1
Basic Sciences	81	17	54	5	5	15	3	12	-	-	66	14	42	5	5

Department	Total PP	Female	Male
Total Funds	$31,221,279	$4,380,156	$26,841,123
Obstetrics/ Gynecology	8,527,778	956,519	7,571,259
Pediatrics	8,948,383	1,034,813	7,913,570
Other Clinical	3,864,884	1,025,398	2,839,486
Basic Sciences	9,880,234	1,363,426	8,516,808

Notes: 1) Biographical data not available on research contracts.
2) Non-Doctorate degrees are on SBIR grants.

TABLE 3.

PP NATIONAL RESEARCH SERVICE AWARDS, FY 1980 - FY 1986

Funds (thousands)

Program Category	Total			F32			F33	F34	T32		
	1980	1983	1986	1980	1983	1986	1980	1980	1980	1983	1986
Total	$1,380	$1,069	$1,681	$242	$154	$282	$35	$9	$1,095	$916	$1,400
High-Risk Pregnancy	353	233	310	152	55	90	-	9	192	178	220
Fetal Pathophysiology	285	133	215	43	42	103	-	-	242	91	112
Premature Labor and Birth	21	36	65	21	36	-	-	-	-	-	65
Disorders of the Newborn	721	668	1,064	25	21	62	35	-	661	647	1,002
Sudden Infant Death Syndrome	-	-	27	-	-	27	-	-	-	-	-

Number of Projects

Program Category	Total			F32			F33	F34	T32		
	1980	1983	1986	1980	1983	1986	1980	1980	1980	1983	1986
Total	27	20	24	13	8	11	1	(1)a/	13	12	13
High-Risk Pregnancy	9	4	5	8	3	4	-	(1)a/	1	1	1
Fetal Pathophysiology	5	3	5	2	2	4	-	-	3	1	1
Premature Labor and Birth	1	2	1	1	2	-	-	-	-	-	1
Disorders of the Newborn	12	11	12	2	1	2	1	-	9	10	10
Sudden Infant Death Syndrome	-	-	1	-	-	1	-	-	-	-	-

Note: 1) In FY 1983 and FY 1986 there were no F33 and F34 funded.
a/ Funds in F34 awarded to supplement grant included in FY 79 count.

TABLE 4.

PP TRAINING BY DEPARTMENT, FY 1980 - FY 1986

Department	FY 1980				FY 1983				FY 1986			
	Fellowships		Train. Grants		Fellowships		Train. Grants		Fellowships		Train. Grants	
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	14	$285,403	13	$1,094,741	8	$153,588	12	$915,523	11	$281,766	13	$1,399,713
Obstetrics/Gynecology	3	69,797	4	405,516	-	-	3	308,377	4	104,016	3	347,537
Pediatrics	6	123,791	8	641,806	3	61,140	8	566,183	4	104,754	9	986,715
Other Clinical	1	16,130	-	-	1	20,040	-	-	1	29,004	-	-
Basic Sciences	4	75,685	1	47,419	4	72,408	1	40,963	2	43,992	1	65,461

INSTRUCTIONS TO THE FETUS

Choose a young, healthy mother of good socioeconomic status who is over 64 inches tall, slender, Rh positive, and has a regular menstrual cycle.

She must not smoke, take drugs, or seek medication. Her family background must be genetically impeccable, and she must seek good antenatal care and a safe place in which to deliver.

So order your own environment and request that you are not born either preterm or postterm. Let not your membranes rupture early, and, above all, enter the world head first with the minimum delay once the journey has started. Having arrived, breathe quickly before they cut your cord, and then ask to be directed to the intensive care unit!

By this you have the best chance to survive the risks of your prenatal life.

Charles P. Douglas
Risks in the Practice of Modern Obstetrics, p. 1
Ed. S. Aladjem, The C. V. Mosby Company, St. Louis 1975